* **DRUG NAMES To Know/Recognize IN PREGNANCY LECTURE** 
  + **OXYTOCICS – Drugs that contract uterine SM muscle**
    - **PROSTAGLANDINS**
      * **DINOPROSTONE**
        + PGE2. In cervix, relaxes SM muscle and stimulates collagenase. In uterus, induces contractions. Augments oxytocin effects so therapy should be stopped prior to administration of oxytocin. SE: Increased GI motility (NVD), hyperstimulation of uterus. Also used in 2nd trimester abortions.
      * **MISOPROSTOL**
        + PGE1 derivative. Used off label for cervical ripening. Advantages: more effective, faster, less need for oxytocin. A lot cheaper than the dinoprostone drugs. Dis: higher incidence of uterine hyperstimulation
      * **CARBOPROST**
        + 15-Me-PGF2a used to inhibit post-partum bleeding when oxytocin or methylergonovine fail. Contracts uterine SM muscle and also causes vasoconstriction. SE: GI (NVD), fever, increased BP and bronchoconstriction. Also used in 2nd trimester abortions.
    - **OXYTOCIN**
      * Acts on G protein-linked receptors that elevate Ca in uterine SM muscle and increases local prostaglandin production. Given IV, IM, or nasally (inactive orally). Short plasma half-life.
        + ↑ force, frequency, and duration of uterine SM muscle contraction, w/ normal relaxation. Sensitivity starts low, but increases throughout pregnancy (30x receptor increase)
        + Contracts myoepithelial cells around mammary alveoli as a result of suckling reflex
        + Weak antidiuretic and vasopressor activity (acts at ADH V2 and V1 receptors)
      * Used in induction of labor when 1.) Pregnancy gone beyond 42 weeks or 2.) When early vaginal delivery will decrease mortality or morbidity for mother or baby (usually bc of premature rupture of membranes). Contraindicated with: cephalopelvic disproportion, abnormal fetal presentation, previous uterine surgery, placental abnormality, umbilical prolapse, fetal distress. Before induction ensure fetal lung maturity and cervical ripening with glucocorticoids and prostaglandins.
      * Maternal monitoring: monitor BP, HR and uterine contractions during infusion
        + Stop if resting uterine pressure > 15-20mmHg, contraction duration >1min, or contraction frequency > 1 per 2-3 min
      * Fetal monitoring: monitor HR and rhythm.
      * Other uses: augment dysfunctional labor, control post-partum hemorrhage, promote milk ejection.
        + Oxytocin challenge test: temporarily decreases fetal blood supply. If fetus healthy, no change in HR. If not healthy, fetal HR decreases
      * Toxicity: uterine rupture, water intoxication
    - **ERGOT ALKALOIDS –** can get ergot poisoning due to prolonged vasospasm (ischemic pain and gangrene of feet, legs, hands and arms. Also dementia with hallucinations and uterine SM muscle contraction 🡪 abortion). Act at alpha adrenergic receptors, DA receptors, and Serotonin (5-HT) receptors (5-HT1A, 5-HT1D, 5-HT2)
      * ***Amine ergot alkaloids (ERGONOVINE and METHYLERGONOVINE)*** importation for effects on uterus. Rapid GI absorption and metabolism
        + Partial alpha adrenergic agonist and 5-HT2 agonist. Strong and prolonged contractions of uterus. Lower doses ↑ force and frequency of contractions with normal relaxation. With higher dose, force and resting tone increase with sustained contractions possible.
        + Less toxic that peptide alkaloids. Primarily used **postpartum** to assist involution and decrease hemorrhage
        + Use limited to a max of 1 week. May be given oral, IM, or IV.
        + SE: rare with IM or oral. Hypertension, nausea and vomiting (CTZ, GI), numbness and tingling of fingers/toes. Prolonged use results in “ergotism:” respiratory depression, hypothermia, convulsions, coma. Prolonged vasospasm leads to gangrene.
      * ***Peptide ergot alkaloids (ERGOTAMINE and DIHYDROERGOTAMINE (DHE))*** important in tx of hyperprolactinemia and migraine (best if given during prodrome). Poor GI absorption and slower metabolism 🡪 longer duration of action.
        + Agonist at presynaptic 5-HT1D receptors (decrease cAMP) on trigeminal nerves innervating cranial blood vessels, inhibiting release of inflammatory/vasodilator peptides (CGRP, substance P). Agonist at cranial vascular SM 5-HT1D receptors
        + Oral, sublingual, rectal, nasal, IV, IM.
        + SE: Nausea/vomiting (metoclopramide used as adjunct), potent vasoconstrictor with prolonged action (numbess,tingling, hypertension, coronary vasospasm, cumulative vasoconstriction with each dose)
        + Contraindications: CAD, PAD, HTN, elevated cholesterol, diabetes, pregnancy (cat X), hemiplegic or basilar membrane. Interacts with CYP3A4 (black box warning): ritonavir, erythromycin, etc can elevate plasma levels 🡪 cerebral or peripheral ischemia.
  + **SUMATRIPTAN –** first line drug used for migraine with or without aura.
    - Selective agonist at 5-HT1D receptors on cranial vascular SM and presynaptic membranes. Little effect on arterial BP or PVR.
    - Not used for prophylactic therapy. Bioavailability 15% due to first pass effect (metabolized by MAO-A).
    - Interactions with MAO-Is, **SSRIs (serotonin syndrome)**, ergot derivatives. Pregnancy cat C (avoid use)
    - SE: unpleasant chest sx (heavy arms, chest pressure – not dangerous due to vaso/bronchoconstriction and muscle spasm). Vasospasm of arteries – can cause coronary vasospasm (contraindicated in pts with CAD)
    - Sumatriptan works faster than dihydroergotamine but there is a higher incidence of migraine recurrence
  + **BROMOCRIPTINE –** selective D2 agonist (decreases cAMP)
    - Used for tx of
      * **hyperprolactinemia** (acts in ant pit)
        + suppresses galactorrhea, can induce regression of tumor
      * acromegaly (lowers GH 50%)
      * parkinson’s (acts in c. striatum)
    - SE: Nausea, GI sx, headache, dizziness, orthostatic hypotension. Give with food to minimize NV
  + **DEXAMETHASONE AND BETAMETHASON**E
    - Glucocorticoids given between weeks 24-34 to promote surfactant production by type II pneumocytes. Stimulates synthesis of fibroblast pneumocyte factor. Last dose should be given >24 hours but <7 days before delivery
  + **TOCOLYTICCS –** suppress premature labor and delivery
    - **MAGNESIUM SULFATE**
      * Tocolytic drug of choice due to low risk of SE and low cost.
      * May act as a Ca antagonist. Inhibits Ach release at uterine NMJs. High concentrations able to inhibit skeletal muscle NMJs leading to weakness, respiratory, and cardiac arrest. 100% renal elimination.
      * SE: transient hypotension and dry mouth. **Pulmonary edema** that could be fatal. Paralytic ileus, somnolence, paralysis.
      * Need to monitor: Mg levels, deep tendon reflexes, renal function (to detect fluid retention, which ↑ risk of pulmonary edema). Mg crosses placenta so newborn may have hypotonia and sleepiness that persists for several days (kidney function not yet fully developed)
      * Contraindications: myasthenia gravis, renal failure, hypocalcemia (intensifies effect of Mg)
      * Calcium gluconate used to treat toxicity
    - **TERBUTALINE AND RITODRINE**
      * B2 selective adrenergic agonists.
      * Major use is tocoloysis. Also used in prophylaxis and tx of acute asthma attack.
      * Oral and IV admin
      * SE: cardiac stimulation
    - **NIFEDIPINE**
      * Tocolytic. Ca channel blocker in SM muscle including uterus.
      * Maternal SE: vasodilation leading to tachycardia, hypotension, facial flushing, HA, dizziness, nausea.
    - **INDOMETHACIN**
      * NSAID (blocks uterine PG synthesis)
      * 2nd line tocolyic
      * Maternal SE: nausea, gastric irritation, interstitial nephritis, increased post-partum bleeding
      * Neonatal SE: renal failure, broncho-pulmonary dysplasia, **respiratory distress syndrome, premature closure of d arteriosus**, necrotizing enterocolitis, intracerebral hemorrhage
  + **METHYLDOPA**
    - Drug of choice for treatment of chronic hypertension during pregnancy. Little effect on uteroplacental flow or fetal hemodynamics
    - Competes with DOPA and DA, NE, and EPI synthesis – produces Me-DA and Me-NE in brain
      * Me-NE is an alpha2 agonist that inhibits SNS outflow to vascular SM and heart**.** Also an α1 agonist, so does not block vasoconstriction or baroreflex completely
    - SE: may lead to sedation and increased prolactin
  + **DRUGS FOR SEVERE PRE-ECLAMPSIA (>180/110) –** requires tx if immediate delivery not chosen. Need to lower BP and prevent seizures
    - **HYDRALAZINE (IV or IM) and LABETALOL (IV)**
      * Often used in combination
      * Hydralazine = vasodilator
      * Labetalol = beta blocker that also blocks alpha receptors
* **DRUG NAMES TO REMEMBER /RECOGNIZE IN NSAID LECTURE**
  + **NSAIDs in general:**
    - NSAIDs inhibit prostaglandin synthesis by inhibiting cyclooxygenase mediated conversion of arachidonic acid to PGH2. Salicylates also play role in NF-KB signaling in inflammatory cascade.
    - Uses:
      * treatment of pain-analgesia (block nerve sensitization by PGE2 and PGI2 for pain that is mild to moderate, ie muscle ache, headache, nerve ache etc. not useful for pain induced by exogenous prostaglandins; differ from opioids no tolerance/dependence and have a ceiling effect; can be used w/ opiods).
      * Treatment of fever – antipyresis (block PGE2 from acting on hypothalamus to change set point of temperature (no effect on normal temp, no effect on temp elevated by exercise ie hyperthermia, no effect on temp elevated by exogenous PGs).
      * Treatment of inflammation in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis (although higher doses aspirin needed to treat inflammation more than for simple analgesia because more than just inhibiting COX2 is involved).
      * Modulation of blood clotting/thrombosis (low doses of aspirin rapidly and irreversibly inhibit platelet TXA2 synthesis by COX1 of platelets, which is needed for aggregation; does NOT block thrombin induced aggregation) so therefore prevents heart attacks and strokes.
      * Close patent ductus arteriosus (PGs needed to keep open. Use indomethacin to close)
      * Tocolysis. Use indomethacin to block PGs from inducing labor (not DOC for this, MgSO4 pref)
    - Adverse effects:
      * GI: bleeding, gastric and duodenal ulcers (since PGE2 protects mucosa)
      * Kidney: can induce kidney failure
      * Reye’s syndrome: hepatic and brain damage when kids take salicylates/aspirin when have influenza or chicken pox (mech unknown, so salicylates gen not used in kids)
      * Uric acid secretion: low 1-2g/d of salicylates DECREASE uric acid secretion by blocking active tubular secretion in kidney. High doses >5g/d of salicylates INCREASE uric acid secretion by stimulate uric acid secretion and block reabsorption. Intermediate dose (2-3g/d) no effect. All doses block probenecid which ↑ uric acid secretion.
      * Close ductus arteriosus; problem in last weeks of pregnancy
      * Hypersensitivity: can produce anaphylactic response esp if have asthma/nasal polyps. Tx w/ epinephrine
    - Toxicity of salicylates:
      * Early stage (35-50mg/dL):
        + CNS: tinnitus, hearing loss, vertigo, emesis (CTZ) resulting in fluid loss
        + Metabolic: uncouple mitochondrial ox phos->higher CO2 production, incr respiration and fluid loss
      * mild-moderate tox (50-80 mg/dL)
        + CNS: hyperventilation -> fluid loss, respiratory alkalosis, NaHCO3 excretion (more fluid loss)
        + Metabolic: heat production by uncoupled mitochondria=hyperthermia, sweating=fluid loss. Glycolysis stimulated-> glycogen depletion and hypoglycemia. Higher CO2, lactate, pyruvate, acetoacetate = metabolic acidosis
      * Severe tox (110-160 mg/dL)
        + CNS: less respiration = respiratory acidosis and then HCO3- depletion. Blood pH decrease and salicylate to brain -> coma.
      * Lethal tox (>160mg/dL)
        + Metabolic: hyperthermia/dehydration and death
        + Kidney: renal failure and death
        + CNS: respiratory failure and death
      * Treat tox: reduce temp, analyze blood, treat dehydration/electrolyte imbalance, charcoal to minimize absorption. Maximize elimination by alkalinizing urine w/ NaHCO3 infusion
  + **ASPIRIN, ACETYL-SALICYLATE, ASA** 
    - Acetylates active site of COX-> irreversible inhibition
    - potent anti-platelet for preventing MI and CVA
  + **SALICYLATE** 
    - Acid is keratolytic and used topically to tx warts.
  + **IBUPROFEN, KETOPROFEN AND NAPROXEN** 
    - Propionic acid derivatives, less intense side effects (OK in kids)
    - Used for pain, fever, menstrual pain and inflammation OTC
    - Ibuprofen half life 1-2h, ketoprofen 1-3h, naproxen 14h (less dosing)
  + **INDOMETHACIN** 
    - Acetic acid derivative
    - Potent inhibitor of COX1, higher incidence of GI effects than aspirin
    - Special short term use only: close ductus arteriosus in premature infants, tocolysis, acute gouty arthritis
  + **SULINDAC** 
    - Acetic acid derivative
    - Prodrug converted to active sulfide in liver; undergoes enterohepatic cycling so actions last 16h
    - Less GI tox than aspirin
  + **DICLOFENAC** 
    - Used for osteoarthritis and rheumatoid arthritis
    - GI toxicity risk similar to aspirin
    - Multiple formulations include rapid release, extended release etc
  + **NABUMETONE** 
    - Low COX1, more selective COX2 so less incidence of GI prob, less ulcers
    - Primarily for antiinflamm for osteoarthritis and rheumatoid arthritis
    - Prodrug converted to active in liver
  + **CELECOXIB** 
    - COX2 specific inhibitor, less GI damage w/o loss of analgesic or antiinflamm properties
    - No effect on platelets
    - Treat: RA, osteoarthritis, juvenile arthritis, ankylosing spondylitis, acute pain and menstrual pain, (previously used to reduce number of polyps in familial adenomatous polyposis until 2011)
    - Possible drug interactions since inhibits CYP2D6 and itself is metabolized by CYP2C9
  + **ACETAMINOPHEN** 
    - NOT an NSAID, no clinically useful antiinflamm properties (very weak effect) (mech seems to be COX2 inhibition but there is much debate on actual mechanism according to Wikipedia, not sure what we were taught in class?)
    - Only shares antipyretic and analgesic properties of NSAIDs (also no tolerance or dependence develops)
    - Different than aspirin: no CNS effects, no Reye’s syndrome, no cardiovascular or respiratory effect, no GI problems, no effect on platelets, no effect on uric acid secretion
    - Toxicity: very little at low doses, hepatotoxicity at 10-15g, death at 20-25g
  + **N-ACETYLCYSTEINE** 
    - At toxic doses of acetaminophen or when taken with alcohol, there is a depletion of glutathione and the toxic intermediate of acetaminophen interacts with cell proteins causing cell death.
    - This drug will provide an alternate substrate for the toxic intermediate and it restores glutathione
    - Will NOT restore damage already done
    - Side effects: N/V/D in oral therapy, if given IV could have anaphylactoid reaction or N/V
* **DRUG NAMES TO KNOW AND REMEMBER IN SEX STEROID PHARMACOLOGY**
  + **GONADOTROPIN RELEASING HORMONES**
    - **GnRH—**secreted by the hypothalamus in pulses—every 1.5 hours🡪 FSH and LH secretion. One cycle induced ovulation in amenorrheic woman or to treat delayed puberty. Continuous release= suppression. Short half-life to work in pulsatile fashion. Synthetic = **GONADORELIN** (Longer half-lives, Higher receptor-binding affinities –more potent drugs).
      * **LEUPROLIDE =** synthetic GnRH but more potent than gonadorelin. Gly at position 6 allow for tighter binding of compounds🡪 leading to hyper potency. Substitution at Gly at position 10 gives longer half lives so long half life. Continuous use to suppresses LH and FSH. Used in in vitro fert to suppress the LH and FSH and then give urofollitropin and hCG for follicle dev and ovulation. Also used to suppress precocious periods, endometriosis (to suppress the overstimulation of estrogen), and prostate cancer and BPH (to suppress growth of cancer by testosterone).
  + **GONADOTROPINS** 
    - **UROFOLLITROPIN** 
      * Menotropin. Only FSH activity. Cheaper than recombinant FSH. Leuprolide is used in vitro to suppress the LH and FSH and then give urofollitropin and hCG for follicle dev and ovulation.
    - **hCG**
      * Isolated from urine of pregnant women. Secreted by placenta🡪 goes into the maternal blood stream🡪 gets secreted by the kidneys in the moms urine. Has LH activity (causes ovulation and progesterone secretion). Cheaper than recombinant hCG. Leuprolide is used in vitro to suppress the LH and FSH and then give urofollitropin and hCG for follicle dev and ovulation.
  + **ESTROGENS** 
    - **ALL USED FOR**:
      * Intractable Dysmenorrhea (not treated by NSAIDS, use progestin w/ it) , Hirsutism, Contraception, Menopause (ERT w/ progestins), Postmenopausal osteoporosis (estrogen + progestin; Second line drugs after bisphosphonates) , HRT (only for 5 years)
    - **ESTRADIOL**
      * Secreted by the ovaries and adrenal glands. Is the dominant estrogen secreted. Dominant estrogen that is controlling the female reproductive cycle. Pharmacologically 17 β estradiol is hardly ever used. Quickly inactivated by liver by conjugation (sulfation and glucoronation). Rapid elimination by kidneys. No oral admin.
    - **CONJUGATED-ESTROGEN**
      * Circa 60% **SULFATED ESTRONE**—even thought they’ve been sulfated they still bind to the estrogen receptor and still work but you have to use them at higher doses. Nice thing about these is they have already passed metabolism by the liver (where they were sulfated) making them orally effective at high concentrations. Common drug: **PREMARIN**® (Wyeth) **PREMARIN + PROGESTIN = PREMPRO**® (Wyeth)
    - **ETHINYL ESTRADIOL** 
      * Synthetic, steroidal estrogen. Dominant synthetic estrogen in oral contraceptive pills Potent agonists at the estrogen receptor. Less-rapidly metabolized by liver 🡪 Longer duration of action. Orally effective
    - **DIETHYLSTILBESTROL (DES)**
      * Moderately potent agonist, Slowly inactivated by liver, orally effective, common in past usage. The structure of this compound doesn't look like it’d be an agonist at the E receptor but the two ethers actually form a benzene ring in space and the structure begins to look like a steroid. Causes vaginal adenosis and vaginal clear cell adenocarcinoma in the children of the mothers who took this.
  + **BISPHOSPHONATES** 
    - **ALENDRONATE**
      * These drugs slow dissolution of hydroxyapatite crystals. They go into bone and replace the pyrophosphate with this🡪it becomes part of the bone crystal structure. The reason they prevent bone loss is b/c these compounds stabilize the bone mineral, they are less likely to be cleaved, etc leading to much slower turn over rate of bone mineral. Doesn't accumulate and no side effects. Used in Paget’s bone disease as well as post menopausal osteoporosis. Used to also treating hypercalcemia that arises from certain kind of Malignancies/cancer. Also shown useful in preventing male vertebral fractures
  + **SERMS** 
    - **TAMOXIFEN**
      * Used to treat **Estrogen receptor positive**—these are not the best kind b/c they grow slower) and they are stimulated to grow by estrogens so you can slow down the growth by txing with a E receptor antagonist. Inhibits estrogen stimulation of cancer growth Can be used on pre- and post-menopausal women with ER- positive tumors. Shown to be just as effective a chemotherapy. Many fewer serious or unpleasant side effects. DOC. Side effects: Hypercalcemia, Bone pain, and Increased risk of endometrial cancer—this is an agonist effect which is weird b/c we call this drug an antagonist. It is acting like an estrogen in the uterus
  + **AROMATASE INHIBITORS** 
    - **ANASTROZOLE**
      * Binds reversibly and is a **competitive non-steroidal** inhibitors of aromatase responsible for conversion of androgens to estrogens. Aromatase is responsible for conversion of androgens to estrogens so if you block this enzyme this conversion does not take place so you don't make estrogens.
  + **PROGESTINS** 
    - **PROGESTERONE**
    - **MEDROXYPROGESTERONE ACETATE**
      * Derivative of progesterone. These are true progestational agents🡪 Can stimulate endometrial secretions and support pregnancy in test animals. Variable androgenic and estrogenic side effects (draw back of these drugs)
    - **NORETHINDRONE & L- NORGESTREL (this one is becoming more popular)**
      * Derivates of nortestosterone. Can stimulate cellular changes in endometrium but CANNOT support pregnancy in test animals b/c these agents do not cause differentiation of the endometrium into the secretory state which is needed for implantation. More effective inhibitors of gonadotropin secretion (so inhibits ovulatory cycle by inhibiting HP axis). Majority of oral contraceptives now use nortestosterone derivative. Late generation analogs have reduced androgenic and estrogenic side effects
  + **ANTIPROGESTINS**
    - **RU486**
      * Anti-progestin. Abortifacient (used to induce abortions). Now used w/ prostaglandin E1 95% effective in inducing abortions. Binds both progesterone and glucocorticoid receptors - preventing gene transcription. Also very good antagonist at glucocorticoid receptor but its typical used to block progesterone receptor Other potential therapeutic uses: Inhibition of progesterone- and glucocorticoid-dependent tumor (like fibroid tumor)s, Cushing’s disease, Post-coital birth control.
    - **FINASTERIDE**
      * Androgens drug. Blocks the enzyme that converts testosterone to DHT in target cells. **PROSCAR**® - Benign prostatic hyperplasia - 5 mg/day = $0.47/mg –CHEAPER. **PROPECIA**® - Male-pattern baldness - 1 mg/day = $1.67/mg
  + CONTRACEPTIVES
    - **Transdermal Contraceptive**
      * Ortho Evra = the patch. Norelgestromin (active metabolite of norgestimate) and ethinyl estradiol. Patch applied weekly. Advantages: Bypasses hepatic metabolism, Lower peak plasma concentrations of drug than COCs, Presumed lower rates of side effects, Better compliance, Comparable failure rates to COCs in typical usage. Disadvantages: Skin allergies --but can rotate patch placement to get around this, Higher steady state concentrations of drug than COCs
    - **Combined Oral contraceptives (COC)**
      * Can be Monophasic: Constant dose of estrogen + progestin over 21 days; Diphasic and triphasic—these were developed to deal with the problem of irregular spotting associated with the monophasic approach. **Diphasic**: progestin dose increased once at approx. day 10, higher dose maintained to day 21.Most common is **Triphasic** - Progestin increased in 2nd and 3rd week of 21 day dosing regimen
      * Progestin-Only (“Mini-Pill”) Low dose of progestin;Taken every day—fairly effective
      * Most commonly used drugs:✶Estrogen**: ETHINYL ESTRADIOL** (Estinyl®)  Progestin: **NORETHINDRONE** (Norlutin®), **L-NORGESTREL** (Ovrette®)
    - **Post coital**
      * **CONJUGATED ESTROGENS**, **ETHINYL**  **ESTRADIOL.** Effective when begun by 72 hours post-coitum (after sex). New studies suggest that 3rd generation progestins, like plan B (L-NORGESTREL) are more effective**.** Effectiveness: 89% (72 hours), 95% (24 hours)  Mechanism – Delays ovulation and sperm migration, found not to disrupt implantation. In women who have ovulated Plan B has no protective effect b/c it doesn't block implantation or fertilization of egg. Strong side effects –these are minimized w/ Plan B though; Nausea, Vomiting, Severe cramps.
    - **Intradermal**
      * **NORPLANT II**® (Jadelle®) = Two flexible capsules containing **NORGESTREL (3rd generation progestin).** Inserted under skin on upper arm or thigh. Require minor surgery with local anesthetic. Effective for up to 5 years. Serum steroid levels are 1/5 to 1/3 of oral contraceptives w/ Fewer side effects. Effectiveness: After One Year: 0.2 failures per 100 women years. After Five Years: 0.8 failures per 100 women years—same as COC
* **DRUG NAMES TO REMEMBER /RECOGNIZE—IMMUNOLOGICS**
  + **METHOTREXATE**
    - DOC for RA. Orally 1xper week. Blocks DHFR to inhibit purine synthesis. Contraindicated in pregnancy (Cat X)! Toxicity offset w/Leucovorin or folate by increasing THF.
  + **LEUCOVORIN** 
    - Given 24 hours after MTX to lower the side effects. It works like folate to increase the THF so that the slower dividing cells can continue division. Also potentiates fluorouracil chemotherapy.
  + **AZATHIOPRINE**
    - Blocks DNA and RNA synthesis. Used for RA, renal transplants. Oxidized by xanthine oxidase therefore drug interaction with Allopurinol which blocks that enzyme. Category D for fetus so causes harm and only can be used if benefits >risks.
  + **ETANERCEPT** 
    - soluble TNFa “receptor” antibody chimera. SC injection 1-2x/week. Used w/or w/o MTX. SE= risk of infections & latent TB, live vaccines contraindicated, neuro issues w/demyelinating diseases (MS), increased malignancy and lymphoma in kids, autoimmunity.
  + **INFLIXIMAB** 
    - Chimeric TNFa Ab.IV infusion once/8 weeks. Used w/MTX for RA, Crohn’s, & ulcerative colitis. SE= risk of infections & latent TB, live vaccines contraindicated, neuro issues w/demyelinating diseases (MS), increased malignancy and lymphoma in kids, autoimmunity.
  + **CYCLOSPORINE**
  + **TACROLIMUS**
  + **SIROLIMUS**
  + **ALLOPURINOL** (see drugs for Gout)
  + **MYCOPHENOLATE MOFETIL** 
    - Used for transplants and off-label for RA. Selectively blocks DNA/RNA synthesis in T cells & B cells bc these need de novo synthesis of GTP. Blocks the proliferation, Ab formation, and lymphocyte activation/migration. SE= GI toxicity, Bone marrow Tox, Category D for fetus.
* **DRUG NAMES TO KNOW/RECOGNIZE FOR GOUT** 
  + **COLCHICINE**
    - Oral drug. ***MECHANISM—***Binds to tubulin (which makes the spindles during cell division) causing dissociation of microtubules (which help move chromosomes during cell division!). Blocks cell division, motility of cells (recruitment), phagocytosis in neutrophils & macrophages. May block macrophage uptake of the crystals 🡪 ↓ inflammatory response. ***TOXICITY – IMPORTANT—***Blocks cell division in GI tract, bone marrow🡪 Produces nausea, vomiting, diarrhea, abdominal pain. Overdose can be lethal, especially when > 4 mg/day given IV. ***USES—*Treatment of ACUTE attack of gout**– “**High dose”🡪**Pain, swelling, redness usually gone in 48-72 hrs. **Maximum total dose**: 1.8 mg over 1 hr. Higher /additional doses provide no additional relief. **NSAIDs** usually preferred as **fewer side effects. Also used for PROPHYLAXIS of acute gouty arthritis** “**Low dose”🡪** Useful in combination with hypouricemic drugs. Discontinue if symptom free for 1 year. **Maximum dose** 1.2 mg per day. ***DRUG INTERACTIONS*** with CYP3A4 and P-gp inhibitors
  + **INDOMETHACIN** 
    - A potent NSAID for short term therapy of gout. Drug of choice, if NSAIDs not contraindicated. Ibuprofen, diclofenac, etc. also effective. As effective as colchicine for an acute attack of gout. If response inadequate, use a glucocorticoid
  + **PROBENACID**
    - Renal handling🡪 90% of this drug is bound to albumin, so most is actively secreted into tubule. We saw this before used to ↓ the secretion of penicillin in order to ↑ it’s half life. Undergoes almost complete non-ionic reabsorption. Plasma t½ = 5-8 hrs because as it gets concentrated down the tubule it has a reasonable half life and its gets reabsorbed. ***ACTIONS* Low doses** block anion secretion in kidney, etc. So at low doses you actually block the secretion of uric acid from the blood into the kidney and we don't want this! Developed to inhibit elimination of penicillin **Higher doses** specifically **block urate reabsorption by acting from the inside of the tubule.** 90% of uric acid is reabsorbed in the PCT of the kidney. **Net effect: increased excretion of urate. *CONSEQUENCES OF THERAPY* ↑ excretion of urate ↑ the risk of uric acid kidney stones** To prevent this: Consume 1500 ml water per day to dilute the urine, Administer 3-7.5 g Na HCO3 per day to alkalinize urine until plasma urate is normal ***and*** tophi have disappeared and DO NOT USE if there is *overproduction* of uric acid b/c **Acute gouty arthritis attacks can be precipitated—DO NOT** initiate treatment until acute attack subsided. Combine with ***low dose*** colchicine, e.g. *Col-probenecid*® To promote uric acid excretion
  + **SULFINPYRAZONE** 
    - Strong organic acid, pK 2.8. Uricosuric action similar to probenecid. Only other uricosuric drug approved in USA, but marketing discontinued
  + **ALLOPURINOL**
    - ***MECHANISM AND PHARMACOKINETICS***
      * Allopurinol looks like a purine & is a competitive inhibitor/substrate of Xanthine oxidase (XO). Allopurinol is oxidized to **oxypurinol** by XO = Result: Allopurinol short t½ = 1-2 hr. **Oxypurinol is a potent non-competitive inhibitor of XO.** Like uric acid, oxypurinol is filtered and reabsorbed 🡪 Result: long t½ = 18-30 hr, long duration of action. ***CONSEQUENCES of THERAPY* Plasma urate** ↓; hypoxanthine↑; xanthine↑ (b/c your blocking their metabolism by XO). Urate in tophi begins to dissolve. More hypoxanthine and xanthine recycled to purines. **Urine urate** ↓; hypoxanthine↑; xanthine↑. Prevents formation of uric acid kidney stones, prevents nephropathy. Although hypoxanthine and xanthine solubility is low, concentration in plasma and urine rarely exceed solubility. These two things are more soluble than uric acid and usually you don't have problems with these but you will still want to maintain ↑ levels of fluids to dilute the urine. ***However;*** to ensure xanthine stones (calculi) **do not** form, urinary output should be maintained at 2L per day and at a neutral or preferably slightly alkaline pH. Incidence of acute gouty arthritis attacks **may actually ↑**  during first months of therapy. **DO NOT** begin therapy during an **acute attack** b/c it will make things worse and. **Use colchicine** (and/or NSAID) until serum uric acid is normal and no attacks for several (3) months, or tophi gone. Attacks decline after tissue stores are reduced—don't need colchicine after this ***ADVERSE REACTIONS* Most serious,** rare but can be **fatal:** Skin rash/fever → i.e. necrolysis, vasculitis, hepatitis, renal failure. ***DRUG INTERACTIONS*** Azathioprine and mercaptopurine (MP). MP is metabolized to thiouric acid by xanthine oxidase so if you use allopurinol the levels of MP in the blood go way up. Administration of allopurinol requires dose↓ to 25-33%. Probenecid and other uricosurics. Inhibit reabsorption of oxypurinol and decrease its half-life ***INDICATIONS*** Patients with **signs and symptoms** of gout, ***not recommended*** for **asymptomatic** hyperuricemia. Patients with leukemia, lymphoma and malignancies receiving chemotherapy 🡪 ↑ purine metabolism that elevates urate
  + **FEBUXOSTAT**
    - Xanthine oxidase inhibitor
    - ***DRUG INTERACTIONS***: drugs metabolized by XO (**Azathioprine**, **Mercaptopurine**, Theophylline)
  + **RASBURICASE**
    - Recombinant form of URICASE from yeast. Used in Pediatric patients with leukemia, lymphoma, and solid tumors undergoing chemotherapy (expected to elevate plasma uric acid b/c ↑ purine metabolism due to ↑ cell death). Short-term therapy that is done while chemo is going on. Adverse effects: Anaphylaxis
  + **PEGLOTICASE**
    - Mammalian URICASE conjugated to PEG (polyethylene glycol). Used in Treatment of gout in adults refractory to XO inhibitors. Have to take IV every 2 weeks. Adverse effects: Severe allergic reaction and sometimes anaphylaxis. Need preinfusion of antihistamines and glucocorticoids to ↓ allergic responses.
* **DRUG NAMES TO KNOW/RECOGNIZE FOR SKIN DISEASES**
  + **TRETINOIN (Retin-A)**
    - Topical for treatment of acne. It is a comedolytic and inhibits keratinization - promotes expulsion of open comedones (promotes expulsion of sebum from the follicle )🡪 Decreases cohesiveness of epithelial cells in follicle & Decreases thickness of *stratum corneum.* Other uses include--diminishes fine lines and wrinkles (*Renova*®), Promotes dermal collagen synthesis, Promotes new blood vessel formation, Promotes thickening of epidermis. Adverse effects: only 10% is absorbed into circulation so minimal/no systemic effects; ↑ susceptibility to sunburn so use sunscreen (15SPF) and protective clothing. Not usually prescribed to pregnant patients b/c of TERATOGENESIS (see isotretinoin contraindication in preg)
  + **ISOTRETINOIN**
    - Systemic retinoic acid. Oral therapy reserved for treatment of severe nodular acne in patients who are unresponsive to conventional therapy, including systemic antibiotics. Very effective tx of acne. Mechanism: ↓ sebum production, ↓ sebaceous gland size, ↓ keratinization, ↓ inflammation.
    - ADVERSE EFFECTS: Similar to those of hypervitaminosis A
      * ON EPITHELIUM/SKIN: Dryness of skin and mucous membranes - results in Dry itchy eyes, nose, mouth, Nose bleeds, inflammation of lips (cheilitis), Less commonly cause Hair loss, peeling of skin from palms and soles, Sensitivity to UV light, use protection against sun, Inflammatory bowel disease
      * HYPERLIPIDEMIA: Elevation of tri-glyceride levels, Sometimes increase in cholesterol (LDL) and decrease in HDLs - needs to be monitored
      * EFFECTS ON BONE FORMATION: Long-term therapy- calcification of ligaments and tendons, Decreased bone mineral density, Pain in joints muscles
      * SUDDEN REDUCTION IN NIGHT VISION: Seems paradoxical
      * PSEUDOTUMOR CEREBRI– RARE: Benign cerebral hypertension, can be mistaken for a tumor 🡪 Leads to edema of optic disk (papilledema), which can lead to permanent blindness—More likely if tetracycline co-administered
      * DEPRESSION - RARE, BUT... Depression and suicidal ideation may be associated with retinoids.
    - CONTRAINDICATION: PREGNANCY--TERATOGENESIS
      * Isotretinoin is a pregnancy category X drug and should not be taken during pregnancy. There is a very high risk of birth defects, e.g. Skull abnormalities, External ear malformation, Facial malformation, Cleft palate, CNS abnormalities, CV abnormalities. *IMPORTANT: To prevent birth defects isotretinoin must be prescribed under the iPLEDGE program—LOTS OF THINGS have to be done to make sure the woman is aware of the side effects and is not at risk of becoming pregnant*
  + **ACITRETIN AND ETRETINATE - SYNTHETIC ANALOGS**
    - They are approved for systemic treatment of psoriasis. Their side effects and contraindications are similar to isotretinoin. **ACITRETIN** is the active metabolite of **ETRETINATE** Etretinate (removed from market) accumulates in adipose tissue and has a very long half-life (120 days) compared with acitretin (49 hours). However, if ethanol is consumed by patients taking acitretin, etretinate is synthesized, consequently, alcohol should be avoided. Also, patients should not become pregnant for at least 3 years after the last dose or donate blood. Mechanism in Psoriasis**:** Inhibits proliferation of epithelial cells, Inhibits keratinization of epithelial cells, Inhibits differentiation of epithelial cells
  + **TAZAROTENE**
    - Tazarotene is a synthetic retinoid. It is a prodrug, which is hydrolyzed to produce a carboxylic acid – tazarotenic acid – the active drug. It is used topically for the treatment of both acne and psoriasis. First topical retinoid approved for psoriasis and wrinkles.
  + **BEXAROTENE**
    - Bexarotene is a drug that is a selective agonist for retinoid X receptors (α, β, γ), and does not activate RAR receptors. It Inhibits growth of tumor cell lines of hematopoietic and squamous cell origin. Used for treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients resistant to one prior systemic therapy. Contraindicated in pregnancy. Side effects: ↑ of TGs, LDL cholesterol & hypothyroidism